Editorial

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Investigating immunity

Recent methods development in immunology has galvanized our understanding of immune responses.

The immune system comprises an intricate network of cells that keep up a state of constant surveillance to protect the body against damage and disease. Immune cells vary widely in their frequency, function, location and molecular state, creating a system of extraordinary complexity. In the last few decades, improved precision, throughput and resolution of methods to dissect immune mechanisms have led to immense strides in our understanding of the immune system and have pushed immunology to the forefront of biomedical research.

Lately, at *Nature Methods* we have increasingly focused our attention on methods development in this field, and thus we are excited to present our first special issue celebrating methods to study immunology.

One of the most established methods for immunological research is flow cytometry, which is used widely for rapid immunophenotyping of distinct cell types on the basis of their surface and intracellular markers. In their Comment, Luc Teyton and colleagues[1] discuss spectral flow cytometry, an emerging method in this area that is based on the key ideas of conventional flow cytometry but now enables high-resolution measurements of single cells by collecting the entire spectrum of emissions from the fluorophores across all wavelengths.

Lymphocytes in the adaptive immune system bear T or B cell receptors (TCRs or BCRs) to recognize antigens presented by major histocompatibility complexes (MHC). The TCR and BCR repertoire is highly diverse in order to protect against a wide variety of antigens; one of the continuing challenges in this field is understanding the diversity and specificity of the immune receptor repertoire. Reviews at *Nature Methods* in the past have discussed the methods for identification of T cell antigens[2] and technologies for TCR sequencing[3]. In the current issue, Tuong and colleagues[4] review the recent computational methods for analyzing immune repertoire sequencing data.

While there are several methods to identify antigens for $CD8^+$ T cells, there are fewer technologies for $CD4^+$ T cells owing to the lower affinity interactions between TCRs and peptide–MHC II (pMHC II). A research paper by Zdinak et al.[5] presents SABR-II, a platform based on chimeric receptors to read out TCR–pMHC II interactions. This study is an extension of the SABR platform[6] for TCR–pMHC I, published previously in *Nature Methods*.

The immune system is an exceptionally dynamic environment where interactions may vary on the basis of temporal, spatial or molecular feedback loops. In a Comment[7], Amber Smith reflects on how mathematical models of the immune system might make immune kinetics more predictable. She suggests that mathematical modeling and experimental validation of hypotheses should be complementary approaches that iteratively improve each other.

While mathematical and statistical modeling have been valuable for predicting immune responses, researchers are now applying machine learning principles to immunological problems. In their Perspective, McMaster et al.[8] discuss the general challenge of predicting TCR binding using the recently described deep learning models for protein structure prediction. They envision the adaptation of AlphaFold for modeling the TCR–pMHC complex and incorporating TCR structure data to predict TCR binding.

Once an immune response is mounted, cells respond via dynamic changes such as proliferation, homing and cytokine production. A previous issue of *Nature Methods* describes TRAP-seq[9], a method to capture cytokine secretion information from single cells. Now, in a research paper[10], Ng et al. report sciCSR, a method to capture the dynamics of the antibody response. During an immune response, B cells undergo class switch recombination (CSR), a process by which they alter the constant region of the expressed BCR to better adapt to the antigenic challenge. sciCSR is a computational tool that uses transcriptomic data to predict the direction of CSR and thus model B cell dynamics.

To pinpoint the factors that drive a biological outcome, Rahimikollu, Xiao et al.[11] developed SLIDE, a machine learning-based method that can identify latent interacting factors from omics datasets. In their paper, they use SLIDE on spatial transcriptomics datasets to uncover the latent factors that regulate the spatial partitioning of immune cells in a mouse allergy model.

Another subfield in immunology that lately has seen substantial methods development is mechano-immunology. These methods allow investigation of mechanical forces during immune interactions. An earlier issue of *Nature Methods* presented a method called BATTLES[12] that uses spectrally encoded beads to mechanically trigger T cells. Now, Huang et al.[13] present a biomimetic antigen-presenting system, or bAPS, that uses hexapod heterostructures to probe T cell activation and signaling.

Much of immunological research is dependent on the use of animal models, and one of the recurring debates in the field is whether these models sufficiently recapitulate the human immune response. With the emergence of organoid technologies, there has been a push toward the development of human immune models such as thymic[14] and tonsil[15] organoids. The team of Christoph Klein has added to this arsenal by developing complex bone marrow-like organoids that mimic the human hematopoietic niche[16].

Despite steady progress, there remain many unresolved methodological challenges, such as the lack of diversity in immunogenomics data[17], the drawbacks of animal models combined with the lack of robust in vitro human systems, and the new limitations of using AI models, to name a few. However, there can be little argument with the importance of immunological research, especially in the aftermath of the COVID-19 pandemic. We are optimistic about the future of immunology and are eagerly watching this space for methods developments that will address open questions in this field.

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